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Development and Characterization of Non-Aqueous based Self Emulsifying Nano Emulsion of Curcumin

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ABSTRACT

This research presented a novel as well as an easy method for a non-aqueous based self-emulsifying nanoemulsion of hydrophobic drug. In this Non Aqueous based self nanoemulsifying drug delivery system (SNEDDS) of curcumin was prepared, and *in vitro* Analysis was done. Oleic acid serves as the oil phase in Curcumin SENE formulations, which also contain Tween 20. PEG 400 as co-surfactants was selected. The preliminary confirmation was done by FTIR spectra and 1603.80cm^{-1} [C=C], 3420.87 cm^{-1} [polymeric OH stretching], 1377.22 cm^{-1} [C=O stretching] was observed. The preformulation study was also done with excellent flow property. Melting point of curcumin was shown at the range of 180-183°C. The λ max of Curcumin was found to be at 424 nm in methanol. Highest solubility of curcumin was found in oleic acid. The primarily confirmation of nano emulsion was done by conductivity test, fluorescence test and Viscosity. Characterization of formulation was done by FT-IR, Droplet size, viscosity, drug content, % Transmittance and robustness study. The spectrum FT-IR of pure drug and self emulsifying nanoemulsion (SENE) was showing the changes.

Keywords: Nanoemulsion; Curcumin; Non-aqueous; Self-emulsifying; Poorly soluble drugs; Hydrophobic; Lipid-based system; Bioavailability.

1. Introduction

According to this research presented a novel as well as an easy method for a non-aqueous based self- emulsifying nano emulsion of hydrophobic drug. At least 40% of the novel medication candidates now being developed are water insoluble and have low bioavailability [1-2]. In instance, the self-emulsifying nano emulsion (SENE), which is well noted for its promise as an alternate method for delivering hydrophobic drugs, has been described as a formulation to combat these issues which have poor oral bioavailability and poor water solubility In the many past year self-nanoemulsifying nanoemulsion attracted the attention of many researcher and pharmaceutical industries. Especially in case of that drugs which are solubility and bioavailability problem. The most important function of the digestive tract is to energy transfer to the tissue in absorbed and usable energy from the food [3].

(A) Self emulsifying drug delivery system (SEDDS)

The most preferred method of medicine delivery for treating specific disorders is the oral route. Low water solubility affects the dissolution and bioavailability of nearly 35 to 40% of recently released medications, leading to considerable intra- and inter-problem variability and a lack of dose proportionality [4].

SEDDS are translucent or transparent, thermodynamically stable, oil and water dispersions with a size range of 50–200 nm.

It has a very low intestinal permeability (absorptive permeability on Caco-2 cell version: 0.07 105 cm/s), which results in its poor gastrointestinal absorption. It is far less soluble (water solubility: 6.5 g/mL) and exhibits excessive affinity to the multidrug efflux transporter Pglycoprotein (P-gp). Similarly, is first-pass metabolized in the liver and/or intestinal wall with the help of cytochrome P450 3A4 (CYP3A4), which may be a factor in its poor (b10%) and highly variable oral bioavailability [5].

(B) Non-aqueous based self-emulsion drug delivery system

In this emulsion, the water is replaced by oil as an inner phase and also disperse phase. This type of Emulsion contains the 20-100nm size of the inner oil globule [6].

(C) Characteristics of SEDDS

1. They may be capable of self-emulsify fast in gastrointestinal fluids & below the have an impact on of gentle agitation.
2. Peristaltic and other gastro intestinal tract movements form a nice o/w emulsion. They can effectively incorporate drug (hydrophobic or hydrophilic) into the oil surfactant mixture. They can be used for both liquid and strong dosage paperwork. In comparison to traditional dosage forms, they require a lower dose of drug [7].

(D) Advantages of SEDDS [8]

1. Improved oral bioavailability, allowing for dose reduction.
2. Additional constant temporal profiles of drug absorption.
3. Selective concentration on drug(s) closer to specific absorption window in GIT.
4. Drug protection from antagonistic environment in gut.
5. Shipping profile management.
6. Less variation, such as food outcomes.
7. Protection of sensitive pharmaceutical materials.
8. Large drug payloads.
9. Dosage form (liquid or solid).

(E) Disadvantage of SEDDS [9]

1. No reliable in vitro model to be had for testing the method.
2. Loss of precise predicative in vitro fashions for evaluation of the formulations.
3. High surfactant attention used in this method which irritates GIT.
4. Risky co-solvent migrates into the shells of tender or hard gelatin tablet.
5. The precipitation tendency of drug on dilution can be better due to dilution effect of hydrophilic solvent.

2. Factors affecting Self emulsifying nanoemulsion (SENE)

(A) Nature of doses of drugs: Drug administered in the huge dose aren't acceptable and comprise in SENE system except people with first-rate solubility in as a minimum one factor of SENE. A drug with low oil and water solubility and a log p value of about 2 is an unsuitable candidate for SENE [10].

(B) Drug solubility in oil phase: Drug solubility in oil phase has impact on the capability of SEDDS to keep in solution. While drug solubilized inside the surfactant and co surfactant diluting SEDDS can end result to lower solvent ability of surfactant and co surfactant [11].

3. Materials and Methods

The following drug, reagents and also chemical used for preparation of self-nanoemulsion of curcumin. All chemical are used for the preparation and characterizations were of analytical grade.

(A) Reagent and chemicals

Glycerol, Ethanol, Oleic acid, Castor oil, Methanol, HCL, Sodium Hydroxide, Tween 20, PEG, Olive oil, Isopropyl myristate, Soyabean oil, Groundnut oil, Corn oil, Liquid parrafin, Potassium dihydrogenphosphate were purchased from Loba Chemical Pvt. Ltd., Mumbai, Merck specialist Pvt Ltd., Mumbai, India, Aahar parivar, Dhanlaxmi Oil Industries, AVA Chemicals Pvt Ltd., Kush proteins Pvt Ltd.,Vasad, Anand.

(B) Equipments

The devices used in during experimentation is Electronic weighing balance, UV-visible-spectrophotometer, FT-spectrophotometer, Particle size analyzer, Centrifuge, Dissolution apparatus, pH meter, Stirring machine, Vortex mixture, Hot air oven.

(C) Drug

The Curcumin used as a drug.

4. Preformulation Study

Preformulation research is a crucial component in the creation of any medication delivery system. It gives the information needed to define the nature of drug, compatibility with surfactant, which provide the information needed for the formulation [12].

(A) Bulk density

The 10 gm of drug was poured in graduated cylinder and volume of drug was measuredby using the formula as mentioned:

Bulk Density = Weight of powder/Volume of powder.

The bulk density was found 0.9g/ml.

(B) Tapped density

The 10 gm of drug was poured into the graduated cylinder and height was measured. The cylinder was tapped 100 times onto the hard surface. The tapping was done and heightwas noted using the formula mentioned is:

Tapped Density=Weight of powder/Tapped Density.

The tapped density was found 1.11 g/ml.

(C) Carr´s Index

The capacity of a powder to reduce in volume under pressure is known as compressibility. It has a tenuous connection to the aforementioned relative flow rate:

Carr's Index = (Tapped Density–Bulk Density)/Tapped Density×100.

The Carr's index was found 13.1%

(D) Hausner's ratio

It is the tapped density ratio that was specified:

Hausner's Ratio= Tapped Density /Bulk Density × 100.

The Hausner's ratio was found 1.17%

(E) Angle of Repose (funnel method)

5 gms of the substance were ingested by funnel. The height of the funnel was set such that the tip just touched the peak of the powder. When the powder was allowed to freely flow through the funnel and onto the surface,

$Ø= \tan^{-1}=h/r$

Where, h = Height of drug, r = Radius of drug, Ø = Angle of repose. The angle of repose was found to be 1.9°.

(F) Result of Preformulation study of Curcumin

The result indicates Good flow ability of pure drug i.e., Curcumin.

5. Results and Discussion

The aim of present project was to formulate Non-aqueous based SENE of curcumin. Novel Non-aqueous based SENE of curcumin which improved solubility and dissolution rate. In this work simple, cost effective and improved the solubility of curcumin by SNEDDS by using oleic acid as oil, tween 20 as a surfactant and PEG 400 used as co- surfactant. The main advantage of SNEDDS was they improve the solubility of drug by reducing particle size, reduction in dose, produce less toxic effect. The fast-dissolving tablet was enhancing the solubility by micronization of drug.

(A) Melting point

It found in the range of 180°C and preliminary confirming the purity of the drug. This suggested that the received sample could be curcumin.

(B) FT-IR

Curcumin exhibits peak in the region of 3500 due to polymeric OH stretching, 1627 cm^{-1} due to aromatic H (-C=C-) H stretching, aromatic C-H stretching 3500cm^{-1}, 1272 cm^{-1} due to C=O, 1240 cm^{-1} due to C-O stretching and 1357.93 cm^{-1} due to FT-IR data showed presence of all peaks of curcumin.

(C) λ max of Curcumin

The λ max of curcumin was found to be 424 nm in methanol, pH 1.2, pH 6.8 and pH 7.4the λ max of curcumin does not change with change pH system.

(D) Solubility study

The solubility of curcumin in oil is a key factor in determining formulation stability. Therefore, SENE's initial requirement is the screening of acceptable oil. Long chain hydrocarbon oil was known to nano emulsify less

effectively than oils with medium or short hydrocarbon chains. So it is found that the curcumin has good solubility in Oleic acid.

6. Preparation of Curcumin SENE

The process is thermodynamically stable because the surfactant must maintain a phase concentration equal to its CMC under the current parameters of temperature, PH, and strength. Safety is a crucial consideration when choosing a surfactant because a large surface area may result in GI pain.

Generally speaking, Non-ionic surfactants have lower CMC than their ionic counterparts. The need that the HLB value be larger than 10 in orders to create an o/w nanoemulsion is a crucial factor in the choosing of a surfactant. When surfactant is diluted with water, the low and high HLB values cause a stable self-Nano emulsion to form [13]. Based on the results of the solubility study and surfactant data, oleic acid as oil, Tween 20 (HLB 16.7) as a surfactant, and PEG 400 (HLB 13.1) as a co-surfactant were selected. Co-surfactant reduces the interface's bending stress and gives the interfacial film the flexibility it needs to adopt the many curves needed to construct a self-Nano emulsion [14].

Finally, the oil phase was added to the curcumin-containing Smix and homogeneously mixed with a vortex mixer. The prepared curcumin non-aqueous based SENE was stored in tightly sealed glass bottles at 25°C, and the stable formulations were investigated further.

7. Evaluation Parameter of Emulsion

(A) Conductivity test

Electricity conduction of water is good. Emulsions with water as a continuous phase will transmit electricity easily, whereas those with oil as a continuous phase won't. Because nano emulsion is o/w, lights do not sparkle. The switch from an oil continuous nanoemulsion system to a water continuous nanoemulsion system is most likely what increased the conductivity of water.

(B) Viscosity

The nanoemulsion had a high viscosity, it indicates that taking the SENE formulation by mouth will dilute it with stomach fluid, increasing its viscosity and decreasing its ability to be absorbed by the stomach.

(C) pH

The pH of the optimized formulation was found to be **5.7**

(D) Refractive index

The R.I of optimized batch was found to be **1.321 ±0.27.** The R.I of optimized batch near to the water indicates transparency of the formulation [15].

(E) Dispersibility study

The curcumin SNEDDS surface at the globule contact will gradually desorbs after being released into the GI tract lumen and dispersed to make a fine emulsion with the GI fluid because the surfactant keeps the oil phase concentration at CMC, the process is thermodynamically stable. Nanoemulsions are crucial because they

avoid precipitation, phase separation, and endless dilution in GI fluid. It can be seen with drugs that are poorly soluble or nanoemulsions that go through phase change. dispersibility investigation carried out in distilled water in order to prevent this circumstance. Grade A and B were regarded to have passed the dispersibility research for a formulation that passed the dispersibility test in water.This is taking place as a result of the SNEDDS made with Tween 20 as the surfactant having a higher HLB value. Higher HLB valve in Tween 20 A good o/w emulsion must be formed with a higher HLB valve. Increased HLB properties support faster emulsification of the oil surfactant mixture in contact with oil. It was found that higher oil concentrations require longer emulsification times due to higher interfacial tension between large amounts of oil and lower surfactant systems, which prolongs emulsification time. The emulsification time studies indicate that the optimized formulation can emulsify with-in 1 min with grade A. They stable at variousdilution (250 ml, 500ml).

(F) Percent Transmittance

Transparency, measured in terms of transmittance (%T), was used to assess the clarity of nanoemulsion. Because oil is the external phase, SENE forms o/w nano emulsions value approaches 100%, the nature formulation is isotropic. As a result, the optimized formulation from ratio (1:1) provides the highest percentage transmittance. Though SENE forms a nanoemulsion in the gastrointestinal tract, which is acceptable to patients, the formulation's isotropy or a transmission rate that is closer to 100% indicates that the globules will be in the micrometer range. Transmittance will rise as surfactant and co-surfactant concentrations rise. Oil globules may decrease the Transparency of a nanoemulsion and the values of %T due to their larger particle size.

(G) Curcumin content determination

The curcumin content of curcumin SENE was found to be 98%.

(H) Zeta measurement

The zeta potential of optimized curcumin SENE was found to be -7.11 mv. The size of the surface charge has a direct impact on the nanoemulsion stability. The potential difference between a closely bonded layer's surface and the zeta potential (electroneutral region and shear plane of solution). The stability of the system was ensured by the 30 mv zeta potential value. High zeta potentialvalues indicate stable formulations that can resist coalescence of particles, whilst formulations with low values of zeta potential may exhibit flocculation of particles when attraction exceeds repulsion.

(I) In-vitro release drug study

Compared to PH 1.2 and PH 7.4, the drug release of pure curcumin was only 73.32% at pH 6.8. After six hours at pH 6.8, the maximum released from the optimized curcumin SENE batch was 97.12%. These findings support the idea that SENE formulations enhance the solubilization and in vitro release of curcumin. The interfacial surface area of the nanoemulsion increases as the size of the droplets decreases. Therefore, the drug small droplet medication releases were more rapid and frequent than those from large oil droplets. The drug release profile of the optimized batch demonstrated that SENE formulations released curcumin in vitro at

a quicker rate than pure curcumin. This is because solubility and dissolution are pH-dependent and there is an ester ionizable group present. After six hours at pH 6.8, the optimized batch maximal release is reached. This behaviour could be explained by a balanced compromise between the ratios of the oil and surfactant combination (30:70). According to these findings, SENE formulations can enhance curcumin solubilization and invitro release.

8. Stability study

With respect to time and temperature, the thermodynamic stability, drug content, and transmittance percentage can all vary slightly. At the conclusion of the 30-day stability testing, phase separation, drug precipitation, and colour change were not observed. The stability study's findings for one month are present.

9. Conclusions

In this project aqueous based self nano emulsifying drug delivery system (SNEDDS) of Curcumin was developed and *in vitro* Analysis was done. Following development, Oleic acid serves as the oil phase in Curcumin SENE formulations, which also contain Tween 20 and PEG 400 as co-surfactants was selected. The preliminary confirmation was done by FTIR spectra which shown 1603.80cm^{-1} [C=C], 3420.87 cm^{-1} [polymeric OH stretching], 1377.22 cm^{-1} [C=O stretching].

The preformulation study was also done with excellent flow property. Melting point of Curcumin show at the range of 180-183°C. The λ max of Curcumin was found to be 424nm in methanol. Highest solubility of Curcumin was found in oleic acid. The primarily conformation of nano emulsion was done by conductivity test, fluorescence test and Viscosity.

The optimized formulation which passed dispersibility test and thermodynamic stability. Characterization of formulation was done by FT-IR, Droplet size, viscosity, drug content, % Transmittance and robustness study. The spectrum FT-IR of pure drug and SENE was showing the changes. It indicates there was interaction between Curcumin and surfactant used in formulations.

The robustness was found in different pH and dilution volume. The Curcumin content of the optimized formulation was found 98%. The formulation of globule size in different media obtain is 1436.9 nm, 911.8 nm in distlled water, 0.1 HCL and pH 6.8 respectively. -7.11mv zeta potential was obtained of the optimized formulation. The dissolution profile of In-vitro Curcumin is significally increased compare to pure Curcumin in pH 1.2, 6.8 and 7.4 buffers. The cumulative releasesof the formulation are 89.60% up to 6 hr. at pH6.8 as compared to pure Curcumin. The stability of formulation was carried out for one month which confirmed formulation in stable.

The present study confirmed that developed Curcumin SENE formulations significantly improve solubility of Curcumin as compared with pure Curcumin.

The present study will definitely draw the attention of the researchers in the future; To understand the individual role of individual lipid and surfactants used for the formulation of self emulsifying drug delivery system as lipid based formulations and also this study will explore the possibilities of loading a wide variety of hydrophobic drugs and plant actives that will be convenient as well as economical too.

Declarations

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Competing Interests Statement

The authors have declared no competing interests.

Consent for Publication

The authors declare that they consented to the publication of this study.

Authors' Contribution

All authors took part in literature review, research, and manuscript writing equally.

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